PATENT COOPERATION TREATY

PCT Rec'd PCT 2005

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

10/544238

Applicant's or agent's file reference 1-1460-PCT	FOR FURTHER ACTION	See item 4 below
International application No. PCT/EP2004/001144	International filing date *(day/month/year)* 07 February 2004 (07.02.2004)	Priority date *(day/month/year)* 11 February 2003 (11.02.2003)]
International Patent Classification (IPC) or national classification and IPC [7] A61K 31/46, 31/4164, 45/06, A61P 11/00		
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 28 October 2005 (28.10.2005)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Agnes Wittmann-Regis Telephone No. +41 22 338 89 70

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

REC'D 13 OCT 2005
WIPO PCT

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/001144	07.02.2004	11.02.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/46, A61K31/4164, A61K45/06, A61P11/00

Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/001144

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/001144

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-4, 12-28 (all partially), 5-11 (completely)

because:

☒ the said international application, or the said claims Nos. 26, 27 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-4, 12-28 (all partially), 5-11 (completely)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/001144

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-4, 12-28 (all partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4, 12-28
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-4, 12-28
Industrial applicability (IA)	Yes:	Claims	1-4, 12-25, 28
	No:	Claims	26, 27 (see separate sheet)

2. Citations and explanations

   see separate sheet

Re Item III.
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Claims 26 and 27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2) Claims 1-4 and 12-28 encompass a genus of compounds defined only by their function ("Anticholinergics" and "TACE inhibitors"), wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.
The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.
The claims cover all combinations of Anticholinergics with TACE inhibitors, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such combinations.
In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Consequently, the search for the first invention has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with SL422.

No opinion of the international Search Authority will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item IV.
Lack of unity of invention

The separate inventions/groups of inventions are:

1) 1-4, 12-28 (all partially)
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with sl422

2) 1-4, 12-28 (all partially)
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with sp057

3) 1-4, 12-28 (all partially)
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with SC903

4) 1-4, 12-28 (all partially)
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with SE205

5) 1-4, 12-28 (all partially)
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with Ro-32-7315

6) 1-4, 12-28 (all partially)
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with BMS-561392

7) 1-4, 12-28 (all partially)
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with PFK 242-484

8) 1-3, 12-28 (all partially), 5
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with a compound of formula 2a

9) 1-3, 12-28 (all partially), 6
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with a compound as specified in claim 6

10) 1-3, 12-28 (all partially), 7
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with a compound as specified in claim 7

11) 1-3, 12-28 (all partially), 8
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with a compound as specified in claim 8

12) 1-3, 12-28 (all partially), 9
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with a compound as specified in claim 9

13) 1-3, 12-28 (all partially),10
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with a compound as specified in claim 10

14) 1-3, 12-28 (all partially), 11
Pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with a compound as specified in claim 11

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

According to Rule 13.1 PCT, "The International application shall relate to one invention only OR to a group of inventions so linked as to form a single general inventive concept".
This is further clarified in Rule 13.2 PCT, which details that "the requirement for unity of invention shall only be fulfilled when there is a technical relationship among those inventions involving one or more of the same corresponding special technical features that defines a contribution which each of the claimed inventions, considered as a whole makes over the prior art".
Rule 13.1-2 PCT requires that claimed alternatives are of a similar nature in having a common property or activity, and either a significant structural element shared by all of the alternatives, or in case a common structure is absent, all alternatives belonging to a recognized class of chemical compounds in the art to which the invention pertains [compare "Administrative Instructions under the PCT", Annex B, Unity of Invention, paragraph (f)].

The present invention is concerned with binary pharmaceutical compositions comprising a first component (1) which is an anticholinergic agent selected from among tiotropium salts, oxitropium salts or ipratropium and a second component (2) which is a TACE Inhibitor selected from the compounds specified on page 2 to page 16. The compositions are useful in the treatment of inflammatory and/or obstructive diseases of the respiratory tract, particularly asthma or chronic obstructive pulmonary disease (cf. page 18, lines 1-4). The whole application does not contain any factual indication that the compositions possess unexpected or advantageous properties, apart from the isolated and experimentally unsupported sentence on page 1, line 32 to page 2, line 1.

Document WO 02/72095 discloses that tiotropium salts are specifically used for treating the inflammatory component of diseases of the upper or lower respiratory tract (especially allergic or chronic rhinitis, bronchiectasis, cystic fibrosis, asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis or fibrosing alveolitis). This document constitute the closest prior art document.

The technical problem which this application sets out to solve vs. the closest prior art can therefore be formulated as "how to provide an alternative composition for the treatment of the aforementioned diseases".

The proposed solution in the present application is the provision of compositions comprising an anticholinergic agent (1) selected from among tiotropium salts,

oxitropium salts or ipratropium salts in combination with one or more TACE Inhibitors (2). Each combination of (1) with (2) constitutes a separate solution to the technical problem, and therefore a different invention. The common concept linking these different inventions is that a combination of anticholinergics and TACE Inhibitors treat the mentioned diseases.

XP009014907 and XP001202131 teach that TNF-alpha has been shown to be involved in COPD and that a novel approach for reducing TNF-alpha levels is by inhibition of TACE and that therefore TACE inhibitors could have beneficial effects in airway inflammatory conditions such as asthma and chronic obstructive pulmonary disease.

Knowing the closest prior art and the mentioned properties of the TACE inhibitors in general, the skilled person would need no special inventive abilities in order to come to the conclusion that a binary composition as in the present claims would solve the technical problem above.
Furthermore it is customary in the clinical development of medicaments to, once a compound has shown therapeutic activity for a disease, test its combination with other agents active against the same disease.

It is concluded that the common concept linking the present inventions is not inventive. Although the different TACE inhibitors or groups of TACE inhibitors in claims 4-11 may share the common property of being Inhibitors of TNF converting enzyme, they do not share a significant structural element, nor do they belong to a single recognized class of chemical compounds in the art to which the invention pertains.

In the present application no further technical features can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions.
Consequently, the present application lacks unity of invention in the sense of Rule 13.1 PCT and the different solutions not belonging to a common inventive concept are detailed as the different inventions listed above.

As the applicant has not had a search report drawn up on the other inventions, the application will be prosecuted on the basis of the invention in respect of which a search has already been carried out, in other words the invention first mentioned in the claims.

Re Item V.

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Attention is drawn to the fact that the present statement expressed as to novelty, inventive step and industrial applicability refers only to matter for which an International Search Report has been drawn up (i.e. only for pharmaceutical compositions, containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts, combined with SL422).

1) INDUSTRIAL APPLICABILITY

Present claims 26 and 27 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2) DOCUMENTS USED IN EXAMINATION

The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1 : WO 02/072095
D2 : EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 12, no. 1 (2003-01-01), pages 5-18, XP009014907
D3 : BRITISH JOURNAL OF PHARMACOLOGY, vol. 135, no. 7 (2002-04), pages 1655-1664, XP001202131
D4 : DRUGS OF TODAY / MEDICAMENTOS DE ACTUALIDAD, vol. 38, no. 9, (2002-09), pages 585-600, XP009022208
D5 : JOURNAL OF MEDICINAL CHEMISTRY, vol. 44, no. 16, (2001-08-02), pages 2636-2660, XP001199586

Unless indicated otherwise reference is made to the passages considered relevant in

the search report.

3) INVENTIVE STEP

The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-4 and 12-28 does not involve an inventive step.

The problem to be solved by the present application is the provision of a medicament for the treatment of respiratory diseases.

The solution proposed by the applicant is a medicament containing one or more anticholinergics, selected from among tiotropium salts, oxitropium salts or ipratropium salts in combination with one or more TACE Inhibitor.

Documents D1 and D4 disclose the use of tiotropium salts for the treatment of asthma and chronic obstructive pulmonary disease (COPD).

Document D5 shows that SL422 inhibits both TACE and MMPs and may therefore provide advantages in the treatment of diseases where those mechanisms are involved, which is the case for COPD and asthma (see D2 and D4)

Therefore the features disclosed in D1 (or D4) and D5 would be combined by the skilled person, without exercise of any inventive skills in order to solve the problem posed. The proposed solution in independent claim 1 thus cannot be considered inventive (Article 33(3) PCT).

Even more the use of a combination of two or more active ingredients with known identical therapeutic use can only be considered as inventive when a surprising effect, an unexpected high synergistic effect or reduced side effects for example, can be assigned in relation to the claimed therapeutic use. In this respect, the present application lacks supportive evidence.

Dependent claims 2-4, 12-28 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).